REMARKS

The Examiner is thanked for the courtesies extended to the undersigned during telephone interviews held on October 28, 2002 and October 29, 2002.

The specification was amended to correct a minor clerical error. A MARKED-UP VERSION OF THE AMENDMENTS TO THE SPECIFICATION is enclosed.

Claims 1 to 11 were rejected under 35 USC 112, second paragraph for the reasons beginning on the middle of page 3 and continuing to the bottom of page 4 of the Office Action.

Step (d) of claim 6 was amended to include features disclosed on page 15, lines 6 to 16 of the specification.

Claim 8 was amended to include features supported in the paragraph bridging pages 16 and 17 of the specification.

Claim 11 was amended to include a feature set forth on page 20, lines 9 to 16 of the specification.

The claims were thus amended to avoid the 35 USC 112, second paragraph rejection.

It is respectfully submitted that the present claims comply with all the requirements of 35 USC 112.

Claim 12 was amended to include the term "PCR" which is supported on page 19, lines 9 to 11 of the specification and in the Example on pages 21 et seq. of the specification and to include the term "probe" which is supported on page 18, line 17 and page 19, line 17 of the specification.

Enclosed is a MARKED-UP VERSION OF THE AMENDMENTS TO THE

CLAIMS.

Claims 1 to 3, 5 to 8 and 11 were rejected under 35 USC 102 as being anticipated by Griffais et al., "K-tuple Frequency in the Human Genome and Polymerase Chain Reaction", Nucleic Acids Research, 19, 3887-3891 (1991) for the reasons set forth on page 5 of the Office Action.

The present invention involves an applied tuple method, which is substantially different from that of Griffais et al. More specifically, Griffais et al. disclose merely a method of obtaining an appropriate primer candidate on the basis of only a primary tuple analysis which corresponds to the first calculation step recited in applicant's claim 6.

In more detail, considering an example of 7-tuple, the method of Griffais et al. carries out a 7-tuple analysis on a target sequence, and selects merely a 7-tuple that has a lower occurrence frequency directly from the result of the analysis. In contrast to Griffais et al., the present invention performs a secondary analysis by carrying out, in addition to this first calculation step, a first extraction step, a second calculation step and a second extraction step.

In the secondary analysis of the presently claimed invention, first, nucleotide sequences that are longer than the 7 tuple (for example, 30 nucleotides), that are present on a target nucleic acid sequence with which a primer, probe or the like, is to be hybridized, are extracted in the first extraction step.

Next, in the second calculation step of the presently claimed

invention, the occurrence frequency of each of the 30 nucleotide sequences is calculated. This calculation is performed on the basis of the results obtained in the preceding primary tuple analysis (the first calculation step). More specifically, the 7 tuples contained in each of the 30 nucleotide sequences are listed. Then, based on the occurrence frequencies of the 7 tuples listed, the occurrence frequencies of the 30 nucleotide sequences are respectively obtained. Here, for example, it suffices only if the occurrence frequencies of all of the 7 tuples listed are multiplied with each other. The occurrence frequency of each of the 7 tuples that are obtained in the preceding primary tuple analysis (the first calculation step) is used.

Then, as the final step, 30 nucleotide sequences that have low occurrence frequencies are selected in the second extraction step of the presently claimed invention.

As described above, the present invention can carry out a 7-tuple analysis similar to that of Griffais et al., however, the method of the present invention obtains the occurrence frequency of each of 30 nucleotide sequences, which is significantly longer than 7 tuples, on the basis of the first analysis. In this respect, the present invention is substantially different from Griffais et al.

The method of the present invention, in which candidate sequences for a primer or probe are obtained on the basis of the two-step analysis described above, has a small operation load on a computer as compared to the case where the analysis of 30 tuples are performed from the beginning, and with this light load, the

calculation does not require a large-scale computer, but it can be done even with a personal computer.

Further, there is a small possibility that a nucleic acid for analysis, that is selected by the method of the present invention, causes mishybridization with a target sequence, in its entire structure of the analysis-use nucleic acid containing, not only the 3'-terminal, but also the 5'-terminal, unlike the case of Griffais et al.

In the case of using a finally selected analysis-use sequence as a primer, it may be sufficient to focus on the 3'-terminal only as in Griffais et al. However, when it is used as a probe, the method of Griffais et al. is insufficient. More specifically, in the case of using the sequence as a probe, not only its 3'-terminal, but also the entire sequence of the probe is important. Therefore, for obtaining a sequence that is used as a probe for detecting a target nucleic acid, the method of the present invention is far superior to that of Griffais et al.

In addition, the sequence obtained by the present invention is superior to that of Griffais et al., because the sequence is obtained by taking into consideration not only the 3'-terminal, but also the 5'-terminal.

Claims 1 to 5 and 8 to 11 were rejected under 35 USC 102 as being anticipated by Rychlik et al., "A Computer Program for Choosing Optimal Oligonucleotides for Filter Hybridization Sequencing and *In vitro* Amplification of DNA", Nucleic Acids Research, 17, 8543-8551 (1989) for the reasons set forth on page 6

of the Office Action.

Rychlik et al. was not applied against claims 6, 7 and 12. Claims 8 to 11 depend directly or indirectly on claim 6. If claim 6 is deemed to be patentable over Rychlik et al., it follows that dependent claims 8 to 11 should also be patentable over Rychlik et al.

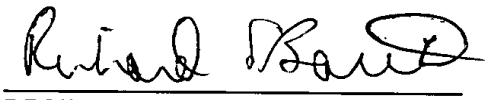
Further, it is respectfully submitted that one of ordinary skill in the art would not consider to combine the novel "tuple" method of claim 6 with the Rychlik et al. factors (1) to (3) set forth on page 6, lines 6 to 15 of the Office Action.

It is therefore respectfully submitted that applicant's claimed invention is not anticipated by the references and are patentable over the references.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Enclosures: (1) PETITION FOR EXTENSION
(2) MARKED-UP VERSION OF THE AMENDMENTS TO THE SPECIFICATION
(3) MARKED-UP VERSION OF THE AMENDMENTS TO THE CLAIMS

MARKED-UP VERSION OF THE AMENDMENTS TO THE SPECIFICATION (SERIAL NO. 09/918,421)

Paragraph bridging pages 14 and 15 of the specification:

--There are twenty four 7-tuples in the 30 nucleotides. Assuming that the twenty-four 7-tuples are numbered 1 to 24 sequentially from the side of the 5' terminal of the 30 nucleotides, and that the frequencies corresponding to the twenty-four 7 tuples calculated above are represented by p1, p2 ..... p24. In this case, the occurrence frequency index of the 30-[necleotide] nucleotide analytical sequence can be calculated by multiplying the frequencies of the twenty-four 7 tuples with each other, as represented by p1 x p2 x ..... p24. The occurrence frequency index indicates how specifically a candidate sequence hybridizes with the ORF to be detected. The lower the value of the index, the higher the specificity. The occurrence frequency index is calculated with respect to all 30-nucleotide candidate sequences present on the target ORF. The candidate sequences are selected based on an appropriate threshold value of the index. The candidate sequences selected in this calculation step are referred to as "low occurrence frequency candidate sequence group". Note that the calculation and graph-drawing can be readily performed by a commercially available computer. Data of the occurrence frequency of individual 30 nucleotide partial sequences are stored in a memory.

MARKED-UP VERSION OF THE AMENDMENTS TO THE CLAIMS (SERIAL NO. 09/918,421)

6. (Amended) A method of determining a nucleotide sequence of an analytical oligo nucleic acid for use in analysis of a nucleic acid, comprising:

(a) a first calculation step of calculating [a] an occurrence frequency of each of n unit sequences occurring on a nucleotide sequence of a target nucleic acid to be analyzed on the basis of a value of 4^n which correspond to all of the n unit sequences formed of n nucleotide sequences [(] , wherein n is an integer of 2 or more[)];

(b) a first extraction step of extracting a sequence having p number of nucleotides and present on the nucleotide sequence of a target nucleic acid, said p is larger than n by m, [(] , wherein m is an integer of 1 or more [)];

(c) a second calculation step of extracting n unit sequences occurring on the candidate sequence extracted in the first extraction step and obtaining [a] an occurrence frequency index of the candidate sequence on the nucleotide sequence of the target nucleic acid on the basis of the occurrence frequency of each of the n unit sequences obtained in the first calculation step; and

(d) a second extraction step of selecting a single or a plurality of candidate sequences, each of the candidate sequences having a low occurrence frequency index based on a threshold value of the occurrence frequency index obtained [in] from the second

calculation step [as potential candidate sequences] , wherein the lower the occurrence frequency index, the higher the specificity.

8. (Amended) The method according to claim 6, further comprising a third extraction step of selecting a candidate sequence having a low stability [on the basis of stability] of a molecular secondary [structure of each of oligo nucleic acid molecules formed of the potential candidate sequences] which is not capable of forming a stable secondary structure and whereby a sequence which is capable of readily hybridizing with a target nucleic acid under hybridization conditions is selected.

9. (Amended) The method according to claim 8, wherein the stability of [a] the molecular secondary structure is [a magnitude] determined by at least one property selected from the group consisting of (i) thermal value of Tm [value] and[/or] (ii) stability of an intramolecular secondary structure.

11. (Amended) The method according to any one of claims [1] 6 to 10, wherein all [necessary] of the calculations involved in steps (a) to (d) are sequentially performed by a computer.

12. (Amended) The method according to any one of claims [1] 6 to 10, wherein said [analytical sequence is a] nucleotide sequence of an analytical oligo nucleic acid is used in (i) a PCR method for detecting a specific nucleotide sequence present in a nucleotide

sequence of a nucleic acid by using an enzyme reaction which requires hybridization reactions of (a) nucleic acid, or [used in] (ii) a hybridization reaction of [the] a nucleic acid employing a probe.